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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,339	HIROSE ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-14,18 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14, 18 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/220,862.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment and entry of the Amendment submitted on 11/18/03 is made. Claims 11-14, 18 and 28 are currently pending.

Specification

1. The disclosure is objected to because of the following informalities:

In the 'Brief Description of the Drawings" on pages 5-6, "Figure 3" should be changed to Figure 3A-D", 'Figure4' should be changed to "Figure 4A-D", 'Figure 5' should be changed to "Figure 5A and B", and 'Figure 6' should be changed to "Figure 6A-C".

In the Amendment to the Specification on page 1, line 2, the related application information should be updated to recite that Application U.S. Serial No. 10/220,862 is now U.S. Patent No. 7,135,559.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 11-14, 18 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is vague and indefinite due to the phrase "or said variation functionally equivalent thereto". It is unclear what structures are encompassed by this language. What function is the claim referencing? Additionally, the language "or a fragment of

said protein or *said variation"* is vague and confusing. What is a 'fragment of a variation'? The metes and bounds of this language cannot be understood. See also 112, first rejections below.

Claim 14 is vague and indefinite due to the term "a transformant". It is unclear what this means. Is this a transformed host cell?

The wording of claim 3 is vague and confusing, i.e., 'consisting of the 126th to 1295th bases in a base sequence of SEQ ID NO: 3 in the sequence listing". Preferred language is "consisting of nucleotides126 to 1295 of SEQ ID NO: 3" .

Claim 18 is vague and confusing due to the phrase "capable of specifically hybridizing". The term 'capable' is not the same thing as actually performing the function. A positive recitation of the function is required. Further, it is unclear what is encompassed by 'specifically hybridizing'. The phrase "specifically hybridizing" is vague and indefinite because hybridization conditions can vary considerably. A number of parameters govern the stringency of the hybridization including the hybridization temperature, hybridization time, washing temperature, washing time, formamide concentration, detergent concentration and salt concentration. Changes in these parameters will affect the specificity of the binding. Thus, in order to ascertain the metes and bounds of the patent protection, the skilled artisan would require knowledge of these specific parameters. The claim does not clearly and unambiguously set forth the appropriate reaction conditions. The rejection may be overcome by clearly setting forth the reaction conditions encompassed by a stringent hybridization, as supported by the disclosure. Claim 18 should also be amended preferred claim language is "an mRNA

consisting of SEQ ID NO: 3". It is not necessary to use the term 'base sequence' or specify the 'sequence listing' and the additional language is confusing.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 11 and 18 read on a product of nature. Claim 11 should be amended to recite "an isolated nucleic acid which encodes a protein..." and claim 18 should be amended to recite "an isolated polynucleotide which...". Appropriate correction is required.

Information Disclosure Statement

5. The information disclosure statement filed 11/18/03 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

NOTE: A list and copies of references were only provided in the IDS submitted 9/28/04. A list was ***not*** provided for the IDS submitted on 11/18/03.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11-14, 18 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 'an isolated nucleic acid sequence encoding a protein comprising the amino acid sequence of SEQ ID NO: 4', 'an isolated nucleic acid sequence consisting of nucleotide 126 to nucleotide 1295 of SEQ ID NO: 3' and plasmids and host cells comprising these nucleic acids, does not reasonably provide enablement for 'genes encoding functionally equivalent variants of SEQ ID NO: 4, genes encoding [random] fragments of said protein or said variation" or plasmids and host cells comprising said nucleic acid.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims contain nucleotide sequences other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; 'however, the specification provides no guidance as to what nucleotides may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as

to which nucleotides could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. To start with the DNA sequence first, this requires even more work on the part of the skilled artisan. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made.

The instant claims are drawn to nucleic acids comprising a sequence which may vary. Selective point mutation to one key residue could eliminate the function of the polypeptide. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. It is unclear what type of activity is to be retained and even more unclear what changes could be made without negatively impacting this activity.

As stated above, Applicants have not shown which nucleotides may be changed without causing a detrimental effect to the protein in which it encodes. The claims allow for unlimited variation and it is unclear what is encompassed by 'functionally equivalent'. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make nucleic/amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Given the lack of guidance contained in the specification regarding acceptable nucleotide substitutions, additions or deletions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112-Written Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 11-14, 18 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth SEQ ID NO: 3 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims which encompass variants, derivatives, fragments and analogs from the full-length sequence.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome.....

and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO: 3, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the

Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore, only "an isolated polynucleotide comprising the nucleic acid sequence set forth in SEQ ID NO: 3', 'an isolated polynucleotide which encodes a protein comprising the amino acid of SEQ ID NO: 4", 'an isolated nucleic acid consisting of nucleotides 126 to 1295 of SEQ ID NO: 3', but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 11, 13, 14, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (Immunogenetics. 1995.41(5): 263-270) corresponding to Genbank Accession No. L38281 and UniProt accession No. P54987.

Lee et al teach a gene which encodes a protein which is a *functionally equivalent variant* to the protein having the amino acid sequence of SEQ ID NO: 4, e.g., LPS-inducible. The nucleic acid sequence taught by Lee et al has a local similarity of 77.6% and an overall similarity of 49.5% to Applicants' SEQ ID NO: 3 and a 70% identity to nucleotides 126-1295 of SEQ ID NO:3 and a 82.9% similarity to Applicant's SEQ ID NO: 4. The recombinant production of the protein is taught. Instant claims 11, 13 and 18 encompass functionally equivalent variants and nucleic acid which encodes generic

fragments of the protein comprising SEQ ID NO: 4. Accordingly, Lee et al anticipates the claims. Additionally, the polynucleotide disclosed by Lee et al would have the capability of specifically hybridizing to SEQ ID NO: 3. The recombinant production of the protein is taught by Lee, e.g, which includes the use of a plasmid and transformed host cell. Sequence alignment available in Public PAIR under the 'Supplemental Contents' tab.

Prior art of record, not applicable:

WO 00/57903 does not qualify as prior art because it was published after the effective filing date of the instant application.

12. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser
Primary Examiner
Art Unit 1645

5/7/07